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ALTHOUGH individuals with Down's syndrome nearly always develop the clinical and pathological features of Alzheimer's disease, some clearly do not become demented despite living into their sixth and seventh decades. Genetic variation at the apolipoprotein E locus has recently been shown to be an important determinant of Alzheimer's disease, with the ε4 allele having been shown to be associated with the disease and, at least in some cases, the ε2 allele being negatively associated with the disease. Here we show, in a series of clinically assessed individuals with Down's syndrome, that the ε2 allele of ApoE is associated with both longevity and the absence of clinical evidence of dementia. These data show that the clinical phenotype of Down's syndrome can be modulated by genes on chromosomes other than chromosome 21. The importance of this observation to the pathogenesis of Alzheimer's disease, both in Down's syndrome and in general, is discussed.

Key words: Down's syndrome; β-Amyloid; Apolipoprotein E; Genetics; Alzheimer's disease; Longevity

Apolipoprotein E ε2 allele promotes longevity and protects patients with Down's syndrome from dementia

M. Claire Royston, David Mann,[1] Stuart Pickering-Brown,[1] Frank Owen,[1] Robert Perry,[2,CA] Ravi Raghavan,[2] Claire Khin-Nu,[3] Stephen Tyrer,[3] Kenneth Day,[3] Richard Crook,[4] John Hardy[4,CA] and Gareth W. Roberts[5]

Departments of Psychiatry and Anatomy, Charing Cross and Westminster Medical School, London W6 8RP; [1]Department of Pathological Sciences and Neuroscience, University of Manchester, Manchester M13 9PT; [2]Department of Neuropathology, MRC Neurochemical Pathology Unit and Institute of Health for the Elderly, Newcastle General Hospital, Newcastle Upon Tyne NE4 6BE; [3]Department of Psychiatry, Northgate and Prudhoe NHS Trust Hospital, Morpeth, Northumberland NE61 3BP, UK; [4]Suncoast Alzheimer's Disease Laboratories, Departments of Psychiatry, Pharmacology, Neurology and Biochemistry, 3515 E. Fletcher Ave, University of South Florida, MDC14, Tampa, FL33613, USA; [5]Department of Molecular Neuropathology, SmithKline Beecham Pharmaceuticals, Harlow CM19 5AD, UK

[CA,CA] Corresponding Authors and Addresses

Introduction

Post-mortem studies have described the universal presence of the pathognomonic hallmarks of Alzheimer's disease (AD) in individuals with Down's syndrome (trisomy 21; DS) over the age of 40 years,[1–4] and that the amount of β-amyloid pathology is variable and related to age and the degree of dementia.[3] Thus in DS, growing old is associated with a progressive pathological process which results in cognitive decline. However, neuropsychological studies of older DS subjects have identified a clinical dementia in only a proportion of cases.[5–9] These contradictory observations could be reconciled if some factor existed which modulated the rate and amount of β-amyloid pathology. Recent studies demonstrate an association between the apolipoprotein E (ApoE) ε4 allele and the earlier age of onset in both sporadic[10–13] and familial[14] AD. Increased amounts of β-amyloid pathology can also be related to the ε4 allele.[15] However, at present there are no data documenting the effects of ApoE genotype on the expression or degree of clinical symptoms of the disease. We examined the ApoE genotype in a cohort of clinically evaluated elderly patients with DS in order to determine the effects of ApoE genotype on the clinical symptoms of dementia. Despite the presence of an active disease process, the ApoE ε2 allele was found to be associated with longevity and preservation of cognitive functioning.

Central to this study is the difficulty of making an accurate diagnosis of dementia of the AD-type in individuals with DS. In DS there is a wide variation in the premorbid intellectual level (verbal and performance) and the level of social/functional skills attained,[6–9] resulting in a variable baseline which makes it difficult to identify and quantify specific cognitive changes

associated with the emergence of dementia. Furthermore, reliable markers identifying the early changes of dementia in DS have not been established since the symptoms of memory dysfunction and disorientation which characterize the early clinical picture of Alzheimer's disease (AD) are not reliable markers of dementia in DS individuals as they also occur in association with their developmental disability. In the literature one approach to solving these problems has been to base a diagnosis of dementia in DS on a change in the level of functioning of an individual patient.[16] Using this approach dementia can be characterized by changes such as reduced speech and comprehension, loss of self help skills, deterioration in social and vocational skills and personality changes.[5,17-20]

The occurrence of AD-type dementia in DS is usually ascribed to the effects of overproduction of amyloid β-peptide (Aβ),[21] caused by a gene dosage effect on the amyloid precursor protein (APP).[22] Mutations in this gene, some of which lead to the overproduction of Aβ from APP, are another cause of AD.[23,24] However, it has recently become clear that the ApoE genotype plays an important role both as a risk factor in the aetiology and as a modulator of the age of onset of AD. Studies have shown that the presence of the ε4 allele predisposes to disease and that of the ε2 allele, in some circumstances, delays onset.[10-14] Furthermore, ApoE appears to modulate the age of onset of disease in a family in which the primary defect is a mutation in the gene which causes increased Aβ production.[24] In this family ε4 homozygotes had an earlier age of onset of dementia than ε3 homozygotes and ε2 heterozygotes had a later age of onset. Essentially similar modulation of age of onset has been observed in other families with APP mutations.[13] Preliminary studies have also indicated that the ε2 allele is associated with longevity in the general population[25] and in DS.[26]

Methods and Subjects

We examined the ApoE genotype in clinically assessed elderly patients with DS from 2 centres: Manchester and Newcastle upon Tyne (UK). A retrospective assessment of the case records was made (including medical and nursing notes) by clinicians blind to the neuropathological data and genotyping results (Table 1). These patients represent a sub-group of individuals reported in previous studies from these centres.[13,20,27] Patients for this study met the following specific inclusion criteria: adequate quality and quantity of clinical information, long stay residence in institutions with good level of training and educational opportunities, no recent changes in institution, trisomy 21 karyotype, screening for, and documented treatment of hypothyroidism and no concurrent significant medical illness which could have contributed to a deterioration in neuropsychological functioning. For subjects from both centres, a diagnosis of dementia was made only if there was clear evidence of a deterioration in self care skills, continence, sleep pattern, occupational skills or the emergence of new dysfunctional behaviours or psychological symptoms. For the purposes of this study a simple division of the patients into a demented and non-demented group was made. ApoE genotyping was carried out using our modification of a standard procedure.[28] The data was examined using the χ^2 statistic (Table 2).

Table 1. ApoE genotype of patients with Down's syndrome and assessment of the presence of dementia

Case	Age	ApoE Genotype	Dementia
A	52	3 4	Yes
B	54	3 4	Yes
C	56	3 4	Yes
D	58	3 3	Yes
E	57	3 3	Yes
F	57	3 4	Yes
G	58	3 3	Yes
H	58	3 3	Yes
I	58	3 3	Yes
J	59	3 4	Yes
K	59	3 4	Yes
L	59	3 3	Yes
M	59	3 4	Yes
N	60	3 4	Yes
P	60	3 3	Yes
Q	61	3 2	No
R	64	3 2	No
S	65	3 3	Yes
T	67	3 3	No
U	68	3 2	Yes
V	69	2 2	No
W	71	3 2	No

Table 2. Effect of ApoE genotype on survival and dementia in Down's syndrome

Genotype	ε3ε4	ε3ε3	ε2ε3	ε2ε2
Mean age at death	57	60	66	68
Demented	8/8	8/9	1/4	0/1

Results and Discussion

No patients were ε4 homozygotes. Those heterozygous for ε4 were youngest at death (mean age 57 years), ε3 homozygotes were intermediate (mean age at death 60 years) and those with at least one ε2 allele were the longest surviving individuals in the study (mean age at death 66). The one patient who was homozygous for ε2 died aged 68. The effect of a single ε2 allele on longevity was highly significant (*t*-test, $p < 0.01$: absence of an ε2 allele, age at death, 58 ± 4 years, $n = 17$: with ε2 allele, age at death, 66 ± 4 years, $n = 5$). The presence of an ε2 allele had a marked relationship to the cognitive state of the patients. Despite the expectation that longevity would be associated with more marked cognitive decline, those patients with an ε2 allele were less likely to develop dementia (presence of an ε2 allele, 1 of 5 demented, no ε2 allele, 16 of 17 demented; χ^2, $p < 0.01$; Table 2).

In the general population the ε2 allele is associated with longevity. The increased life span of DS patients who carry the ε2 allele reported in this and previous studies[25] is therefore unsurprising. Ageing is the most important risk factor associated with the development of AD[26] and studies on DS patients have clearly demonstrated a correlation between age and the amount of β-amyloid neuropathology.[5] Thus, one might predict a significant trend for DS subjects with an ε2 allele (by virtue of their increased life expectancy) to exhibit the highest accumulation of β-amyloid neuropathology and therefore be at greatest risk of developing an AD-type dementia. Paradoxically, our study does not support this hypothesis. Subjects with at least one ε2 allele were significantly less likely to develop an AD-type dementia. Our data demonstrate that the trisomy 21 phenotype can be modified by genes on other chromosomes. It is likely that other characteristics of the DS phenotype are similary variable. In addition our data show a way of integrating the genetic and pathological data and resolving the contradictions between neuropathological and neuropsychological studies on older DS patients. A large part of the scatter in the various data sets for older DS patients is probably explained by variability in their ApoE genotype.

The mechanism underlying the association between ApoE genotype and the development of AD-type neuropathology is uncertain. It has been reported that the ApoE proteins have a variable binding affinity for soluble Aβ (binding affinity of ε4 > ε3[24]). This may enhance the stability of insoluble β-amyloid. If the ε2 binding affinity is lower it could explain the effect in altering the rate of deposition of β-amyloid and thereby the delayed onset of dementia reported in this study. However, both DS and AD patients with ε2 alleles can become demented and as we have noted previously,[25] develop both β-amyloid and tau related pathologies. We interpret this to indicate that the role of the ApoE genotype is probably one of modulating the basic disease process rather than playing a causal role. However, this does not diminish the importance of this interaction as a potential therapeutic target.

Our data indicate that, in patients at risk of developing, or in the early stages of Alzheimer's disease, determination of the ApoE genotype and in particular the possession of an ε2 allele may well offer a considerable advantage in determining the likely prognosis of a patient. Such prognostications will have considerable utility in the design planning and implementation of clinical care of DS and AD patients. In addition because the clinical expression of dementia is related to the progression and degree of pathology, determination of the ApoE genotype will provide guidance in the selection and implementation of modes of therapeutic intervention both in clinical trials and practice.

Conclusion

Genetic variation in the ApoE gene is an important factor in determining the lifespan of persons with Down's syndrome and determining whether they will become clinically demented. This is important for the development of an understanding of the pathogenesis of all cases of Alzheimer's disease, and is also important because it shows that the phenotype of Down's syndrome is influenced by genes on chromosomes other than chromosome 21.

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